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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/668,672	09/23/2003	Samuel L Stupp	NANO 105 US2 (NU 22074)	1810

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EXAMINER	
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ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/668,672	STUPP ET AL.	
	Examiner	Art Unit	
	SUZANNE M. NOAKES	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,15,17 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,15,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/03/2008 & 01/07/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendments to the claims in the reply filed 01 December 2008 are acknowledged. Applicants have canceled claims 14. Thus, claims 13, 15, 17 and 18 are pending and subject to Examination.

Information Disclosure Statement

2. The information disclosure statements (IDS) submitted on 03 September 2008 and 07 January 2009 have been considered by the examiner. See initialed and signed PTO-1449's.

Withdrawal of Rejections/Objections

3. Any rejection/objection recited in the previous Office action and not explicitly restated below is hereby withdrawn.

The rejection of claims 13-15, 17 and 18 are rejected under 35 U.S.C. 112 second paragraph, recited in the previous Office action in Section 6, is withdrawn in view of the amendments to the claims cancelling the term "tissue engineered material" and also requiring the peptide amphiphile composition comprise both SEQ ID NO: 1 and 2.

4. The rejection of claims 13-15, 17 and 18 are rejected under 35 U.S.C. 112 second paragraph, recited in the previous Office action in Section 8 is withdrawn in view of the amendments to the claims to recite "a patient in need of axon outgrowth of a neuron".

5. The rejection of claim 13 under 35 U.S.C. 112, first paragraph, scope of enablement is withdrawn in view of the amendment to the claim which requires that both SEQ ID NO: 1 and 2 be present in the composition.

New Rejections/Objections – Necessitated by Amendments

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 13, 15, 17 and 18 are rejected under 35 U.S.C. 103(a) as being obvious over Stupp et al. (US 7,371,719 – the equivalent US Pregrant Publication 20040001893 was cited on IDS from 02/16/2007) which has a priority date of 02/15/2002.

The applied reference has two common inventors, Samuel I. Stupp and Jeffrey D. Hartgerink, with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130

stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The instant claims, as amended, are drawn to a method of treating a patient in need of axon outgrowth of a neuron with a nanofibrous material by injecting said patient at a particular site with a peptide-amphiphile composition wherein said peptide-amphiphile composition promotes axon outgrowth of a neuron and wherein said peptide-amphiphile composition which forms a nanofibrous material is formed by combining a peptide-amphiphile that comprises SEQ ID NO: 1 and 2 (claim 13); at concentrations of 2-30 mg/ml (claim 15); wherein said amphiphiles are present in charge equivalent ratios, wherein the charge equivalent ratio requires to parts SEQ ID NO: 1 to 1 part SEQ ID NO: 2 (claim 18).

Stupp et al. teach peptide-amphiphile (PA) compositions which can be used for various applications and methods. It is specifically taught (see column 4, lines 34-40):

> It can also be an object of the present invention to provide peptide amphiphile compositions comprising two or more oppositely charged peptide components, each such component as can further include the same or a differing bioactive epitope sequence, for subsequent biomedical applications including without limitation either in vitro or *in vivo drug delivery, cell therapies or tissue engineering*.

Also it is taught that specific peptide amphiphiles form a gel which is comprised of nanofiber networks/micelles of said peptide amphiphiles: (see column 8, last paragraph to column 9, lines 1-16)

> In part, the present invention also provides a sol-gel system including 1) a polar or aqueous solution and/or containing of one or more of the amphiphile compounds or compositions described herein, and 2) a factor or reagent sufficient to induce assembly, agglomeration of gelation under neutral or physiological conditions. Such gelation and/or self-assembly of various PA compositions into **micellular nanofibers** can be achieved under substantially neutral and/or physiological pH conditions through drying, introduction of a mono- or multivalent metal ion and/or the combination of differently charged amphiphiles. The approach of using differently charged amphiphiles can also be utilized to deliver in the self assembling **nanofibrous system** two or more bioactive molecules, each bearing different charges and this way combining the gelation technology with the delivery of multiple biological signals. Such facile factors, as described more fully below and in several of the following examples, can extend the sol-gel system and/or methodology of this invention to a variety of medical applications. These and other aspects of the present invention can be described with reference to the PA compositions provided in Table 2, below, with further reference to FIGS. 1, 10A-B and Table 1, above

Notably, Table 2 teaches peptide amphiphile 24 (PA24) which has a net overall charge of +2 and is 100% identical to the instant SEQ ID NO: 2; also taught is peptide amphiphile 25 (PA25) which has a net overall charge of -1 and is 100% identical to the instant SEQ ID NO: 1. With regards to peptide amphiphiles 24 and 25, and thus instant sequences SEQ ID NO: 2 and SEQ ID NO: 1, respectively, the YIGSR peptide sequence is found within PA 24/instant SEQ ID NO: 2 and the IKVAV peptide sequence is found within PA 25/instant SEQ ID NO: 1. Stupp et al. teach the following regarding these particular peptide sequences and peptide amphiphiles 24 and 25 (see column 9, lines 46-67).

> The peptide epitopes on molecules 22-25 demonstrate the biomedical potential of the self assembling systems described here. RGD is the well known cell adhesion ligand found in fibronectin while *IKVAV, SEQ ID NO:32, and YIGSR, SEQ ID NO:33, are laminin sequences known to interact with mammalian neurons. IKVAV, SEQ ID NO:34, promotes neurite outgrowth in mammalian neurons, while YIGSR, SEQ ID NO:35, plays a related role in neuronal cell-substrate adhesion*. While these and other bioactive epitope sequences can be used to effect cell adhesion, proliferation or differentiation and related outcomes, in a broader context, the PA compounds/compositions and related methods of this invention can be used in conjunction with any epitope sequence capable of cellular interaction and/or binding to a cellular membrane receptor. In particular, peptide amphiphiles 23 and 25 have a net negative charge at neutral pH, whereas PH 22 and 24 have a net positive charge. *Electrostatically driven co-assembly between PA compounds 24 and 25* as well as 23 and 22 *provide mixed nanofibers that simultaneously present two biological signals in a cellular environment*.
>
> It is further taught (see column 11, lines 46-64):
>
> Accordingly, such a system can be used in conjunction with a drug, medication or other therapeutic agent, as would be understood by those skilled in the art: *the subject drug or therapeutic agent can be provided with or introduced to an appropriate aqueous or polar medium separately or in conjunction with one or more PA compounds*. Introduction of a reagent and/or factor induces nanofiber assembly and/or gelation, incorporating such a drug/agent therein, if hydrophobic, or as bound to or sorbed on the surface thereof, if hydrophilic. Disassembly or solubilization of the nanofibrous network or gel can release or deliver the drug/agent as or where required. As would be understood by those skilled in the art made aware of this invention, a range of both hydrophobic and hydrophilic drugs/agents can be utilized herewith. In particular, with regard to the peptide epitopes thereof, hydrophilic growth factors, co-factors and/or activators can be adsorbed on, delivered with and/or released by the PA compounds/compositions of this invention.

Example 7 teaches that the peptide amphiphiles 24 and 25 from Table 2 (which are the same as instant SEQ ID NO: 1 (contains IKVAV) and SEQ ID NO: 2 (which contains YIGSR)) were mixed and dissolved at concentrations of 5 mg/ml and that the mixture formed a birefringent gel, which is considered a "nanofibrous material". It is further noted in Example 9 that what drives the formation of the peptide-amphiphiles into said

gel is the elimination of the charges, e.g. one +2 peptide amphiphile (e.g. one PA 24/instant SEQ ID NO: 2) would require two molecules of PA25/SEQ ID NO: 1, which has a charge of -1, to cancel out the overall charge. Thus, inherently, the amphiphiles were necessarily present in a 2 to 1 ratio of SEQ ID NO: 1 to SEQ ID NO: 2 (meets claims 17 and 18).

It is finally taught: (see column 11, lines 28-46):

> Self-assembly and/or gelation under physiological conditions, as induced by the preceding factors, raise numerous implications regarding end use application and effect. Without limitation, with reference to the preceding, a binary or higher PA mixture makes available a sol-gel system for the formation of micellular nanofibers in a aqueous environment at neutral and/or physiological pH conditions. As discussed elsewhere herein, such a combination of two or more PA compounds can be used to assemble nanofibers with a range of residues providing a corresponding variety of concurrent chemical or biological signals for cell adhesion proliferation, differentiation and the like, yielding enhanced properties with regard to tissue engineering or regenerative applications. Alone, or in conjunction with one or more of the other factors discussed herein, it is contemplated that preferred medical or therapeutic embodiments of such a system or methodology ***can be implemented upon step-wise introduction and mixing of the subject PA compositions, with in situ gel formation.***

Thus, Stupp et al. teach a peptide-amphiphile composition comprising SEQ ID NO: 1 and SEQ ID NO: 2 in concentrations that are between 2 and 20 mg/ml and which are expected to be present in charge equivalent ratios (e.g. one part SEQ ID NO: 2 and two parts SEQ ID NO: 1) in order to produce a gel system which is a nanofibrous material which is taught can be used in *in vivo* drug delivery methods which would be used to treat patients in order to promote neurite outgrowth in mammalian neurons and neuronal cell-substrate adhesion because the specific peptide amphiphiles of SEQ ID NO: 1 and SEQ ID NO: 2, and specifically IKVAV which is found in SEQ ID NO: 1

promotes neurite outgrowth in mammalian neurons, while YIGSR, found in SEQ ID NO: 2, plays a related role in neuronal cell-substrate adhesion. Furthermore, it is taught that each peptide amphiphile can be injected in a step-wise manner with gel-formation occurring *in situ*.

Stupp et al., however, do not teach a method of injecting patients in need thereof (in need of axon outgrowth of neuron) with such a composition.

Nonetheless, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to utilize the sol-gel system which forms nanofibrous material and which contains SEQ ID NO: 1 and 2 (PA24 and 25 -Table 2 - are 100% identical to instant SEQ ID NO: 1 and 2) in a method for which the composition was designed to be used. Specifically, said skilled artisan would be motivated to treat patients in need thereof with a composition for which it was designed. It would be obvious to use said composition to treat patients that are in need of axon outgrowth of a neuron because this is precisely what SEQ ID NO: 1 does (and SEQ ID NO: 2 aids in the neuron adhesion). Furthermore, it would be obvious to administer said composition to said patient in need therefor in a variety of techniques available to one skilled in the art including by way of injection, especially given that it is taught that introduction of the peptide amphiphiles can be introduced in a step-wise manner, e.g. each PA injected separately, so as formation of the nanofiber network occurs *in situ* (otherwise, the composition would be in the form of a gel which would be more difficult, albeit not impossible, to inject).

Response to Arguments

8. Applicant's arguments filed 01 December 2008 have been fully considered but they are not persuasive.

It is asserted that the '719 patent of Stupp et al. does not specifically describe a method of treating a patient in need of axon outgrowth of a neuron with a nanofibrous material by injecting a composition of a peptide amphiphile comprising SEQ ID NO: 1 and a peptide amphiphile comprising SEQ ID NO:2. The claim-designated peptide amphiphiles self-assemble into nanofibrous material, which promote axon outgrowth of a neuron. Applicants submit that this claim language distinguishes from the '719 patent. In particular, the '719 patent does not describe the injection of two peptide amphiphiles into a patient in need of axon outgrowth, where the peptide amphiphiles form a nanofibrous material.

The Examiner, however, has withdrawn the 35 U.S.C. 102 rejection or record in favor of a 103 rejection based upon Applicants amendments to the claims. However, it is asserted that the '719 patent suggests and motivates one skilled in the use the composition which is taught in a method for which it was specifically designed to be used. With regard to the limitation of injection, the instant specification states that the two peptide amphiphiles, e.g. SEQ ID NO: 1 and 2 would necessarily have to be injected separately into the site desired (otherwise, as noted above, gel formation occurs nearly instantaneously which makes injection more difficult). The '719 patent specifically notes that *in situ* gel formation by step-wise introduction of the peptide amphiphiles may be desired and can be achieved by "step-wise introduction" of the

desired peptide amphiphiles. Thus, given what is taught in said '719 patent, it would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to utilize the composition as taught in a method for which it was specifically designed to treat patients in need of axon outgrowth of a neuron and to deliver said composition in manner which has been described. It would be obvious to one skilled in the art to utilize a variety of techniques such as injection to introduce said peptide amphiphiles in this step-wise manner for *in situ* gel formation to occur.

Conclusion

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUZANNE M. NOAKES whose telephone number is (571)272-2924. The examiner can normally be reached on 7.00 AM-3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SUZANNE M. NOAKES/
Primary Examiner, Art Unit 1656
06 February 2009